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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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020322
SNELL & WILMER
ONE ARIZONA CENTER
400 EAST VAN BUREN
PHOENIX AZ 85004-0001

HM12/1214

EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	7

DATE MAILED: 12/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/498,135	STONE, JOHN F.	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed November 11, 2000. Currently, claims 1-13, 15-17 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the new grounds of rejection.

3. This action contains new grounds of rejection necessitated by amendment.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 6-8, 11, 13, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherry et al. (Mutation Research, Vol. 275, pg. 57-67, 1992) in view of Marcon et al (Mutation Research, Vol 45, pg 155-166, September 1999).

Cherry et al. (herein referred to as Cherry) teaches facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent, marking some of the chromosome fragments, and analyzing the fragments to determine

whether cells were affected by the disease. Specifically, peripheral blood lymphocytes from patients with Alzheimer's disease (AD) and controls were grown in culture for 72 hours with phytohemagglutinin (mitogen)(pg. 60, col. 2)(limitations of Claims 2 and 3). Then the cells were treated with bleomycin, which causes an activated oxygen radical, or with methyl methane sulfonate (MMS) (chromosome damaging agents)(abstract)(limitations of Claim 6-7, 13, 15). Then cells were harvested, fixed on slides, and marked with Giemsa stain (limitations of Claim 4). 50 cells/ patient were scored for chromosome damage. Comparison between patients with Alzheimer's and control patients was performed to determine whether a significant difference existed (limitations of Claims 14, 16 and 17). As seen in Figure 1, bar charts are presented which show significant differences between AD women and control women with bleomycin (pg. 62). Cherry teaches that when considering women, bleomycin is a very effective marker for AD (pg. 65, col. 1).

Cherry does not explicitly teach a method of diagnosing Alzheimer's using interphase cells.

However, Marcon et al. (herein referred to as Marcon) teaches a method of detecting chromosome damage and aneuploidy detected by interphase multicolour FISH in benzene-exposed shale oil workers. Marcon teaches the simultaneous detection of both chromosome breakage, involving damage-prone pericentromeric regions and hyperploidy in interphase cells (abstract). Marcon teaches that cultured lymphocytes of the benzene-exposed workers compared to the unexposed controls were modestly increased frequencies of breakage, suggesting an expression of

premutagenic lesions during the S-phase in vitro (abstract). Myeloid leukemia-inducing agents includee benzene (pg 164, col. 1). Macron also teaches that tandem labelling FISH can be usefully applied to human biomonitoring at interphase in different cell types (abstract). Macron teaches that the methodology was applied to interphase blood smear cells and culture lymphocytes, demonstrating the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2). Marcon teaches that "one advantage to the application of tendem labelling is the ability to detect chromosome changes in interphase nuclei, in addition to metaphase cells. As a result different celly types including those not amenable for metaphase analysis, can be investigated" (pg 163, col. 2). Further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cherry to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the

method of Cherry to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell.

5. Claims 1-2, 4, 11, 13, 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (Mutation Research, Vol. 256, pg. 21-27, 1991) in view of Marcon et al (Mutation Research, Vol 45, pg 155-166, September 1999).

Chen et al. (herein referred to as Chen) teaches facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent, marking some of the chromosome fragments, and analyzing the fragments to determine whether cells were affected by the disease. Specifically, Chen teaches a sampling cells and transforming by Epstein-Barr virus to establish lymphoblastoid cell lines (pg. 22, col. 1). Cells were cultured in agar and subjected to irradiation (a chromosome damaging agent)(pg. 22, col. 2)(limitations of Claim 2). The colonies with 50 or more cells were isolated to determine the frequency of radiation-inducted aberrations. The cells were fixed, spread on slide, and stained with Giemsa to mark the chromosomes (pg. 22, col. 2)(limitations of Claim 4). Upon studying of the cells, a higher frequency of chromosome-type lesions was observed in AD cells, indicating the cells from AD patients were more radiosensitive than normal patients (pg. 25, col. 1). 12 or 14 patients show sensitivities greater than cells from age-matched controls (pg. 26, col. 1).

Chen does not explicitly teach a method of diagnosing Alzheimer's using interphase cells.

However, Marcon et al. (herein referred to as Marcon) teaches a method of detecting chromosome damage and aneuploidy detected by interphase multicolour FISH in benzene-exposed shale oil workers. Marcon teaches the simultaneous detection of both chromosome breakage, involving damage-prone pericentromeric regions and hyperploidy in interphase cells (abstract). Marcon teaches that cultured lymphocytes of the benzene-exposed workers compared to the unexposed controls were modestly increased frequencies of breakage, suggesting an expression of premutagenic lesions during the S-phase in vitro (abstract). Myeloid leukemia-inducing agents includee benzene (pg 164, col. 1). Macron also teaches that tandem labelling FISH can be usefully applied to human biomonitoring at interphase in different cell types (abstract). Macron teaches that the methodology was applied to interphase blood smear cells and culture lymphocytes, demonstrating the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2). Marcon teaches that "one advantage to the application of tendem labelling is the ability to detect chromosome changes in interphase nuclei, in addition to metaphase cells. As a result different celly types including those not amenable for metaphase analysis, can be investigated" (pg 163, col. 2). Further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chen to predict the AD state of individuals with the method of Marcon for determining chromosome

damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Chen to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell.

6. Claims 1-6, 11-13, 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parshad et al (PNAS, Vol. 93, pg. 5146-5150, May 1996) in view of Marcon et al (Mutation Research, Vol 45, pg 155-166, September 1999).

Parshad et al. (herein referred to as Parshad) teaches a method for facilitating disease diagnosis by exposing cells of a suspected diseased patient to a chromosome damaging agent, marking some of the chromosome fragments, and analyzing the fragments to determine whether cells were affected by the disease. Specifically, Parshad teaches sampling skin fibroblasts and blood from patients diagnosed with Alzheimer's and control patients. The heparinized blood was mixed with phytohemagglutini (mitogen) and incubated for 48 or 68 hours (limitations of Claims 2 and 3). The lymphocyte cultures were subjected to either fluorescent light or 254 nm UV light (chromosome damaging agent that causes free radical-induced DNA damage)

(pg. 5147, col. 1, para. 3 and 4)(limitations of Claim 6). Moreover, the cells were then treated with beta-cytosine arabinoside (araC) or caffeine (repair retarding agents) (limitations of Claim 5 and 12). Chromatid breaks were quantitated using cytogenetic analysis of metaphase cells.

Prashad does not explicitly teach a method of diagnosing Alzheimer's using interphase cells.

However, Marcon et al. (herein referred to as Marcon) teaches a method of detecting chromosome damage and aneuploidy detected by interphase multicolour FISH in benzene-exposed shale oil workers. Marcon teaches the simultaneous detection of both chromosome breakage, involving damage-prone pericentromeric regions and hyperploidy in interphase cells (abstract). Marcon teaches that cultured lymphocytes of the benzene-exposed workers compared to the unexposed controls were modestly increased frequencies of breakage, suggesting an expression of premutagenic lesions during the S-phase in vitro (abstract). Myeloid leukemia-inducing agents includee benzene (pg 164, col. 1). Macron also teaches that tandem labelling FISH can be usefully applied to human biomonitoring at interphase in different cell types (abstract). Macron teaches that the methodology was applied to interphase blood smear cells and culture lymphocytes, demonstrating the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2). Marcon teaches that "one advantage to the application of tendem labelling is the ability to detect chromosome changes in interphase nuclei, in addition to metaphase cells. As a result different celly types including those not amenable for metaphase analysis, can be

investigated" (pg 163, col. 2). Further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Prashad to predict the AD state of individuals with the method of Marcon for determining chromosome damage in interphase cells. The ordinary artisan would have been motivated to have analyzed interphase cells using the method of Marcon for the expected benefits of the feasibility of using this approach to simultaneously investigate different cell types (pg 156, col. 2) including those different cell types including those not amenable for metaphase analysis, and further, "this allows cells with different metabolic capabilities and turn-over, or the same cell population in different phases of the cell cycle, to be studied" (pg 164, col. 1). The ordinary artisan would have realized that expanding the method of Prashad to include studying interphase cells as taught by Marcon would vastly increase the information gained with respect to the chromosome breakage in a cell. Thus, based upon the teachings in Prashad that significant differences between AD and controls were observed when cells were treated with radiation and caffeine (pg. 5147, col. 2), the ordinary artisan would have been motivated to test unknown interphase samples to determine the AD status of the individual.

7. Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherry et al. (Mutation Research, Vol. 275, pg. 57-67, 1992) in view of Marcon

(Mutation Reserch, Vol 445, pg 155-166) as applied to Claims 1-4, 6-7, 11, 13-17 above, and further in view of Gorczyca et al (Cancer Research, Vol. 53, pg. 1945-1951, April 1993).

This rejection is applied to a narrower embodiment where Alzheimer's is detected using terminal deoxynucleotidyl transferase and nick translation assays.

Cherry does not specifically teach labeling the chromosome fragments with dNTP and exposing the fragments to a fluoresceinated material.

However, Gorczyca et al. (herein referred to as Gorczyca) teaches a method of detecting DNA strand breaks by in situ terminal deoxynucleotidyl transferase and nick translation. Gorczyca teaches sampling peripheral blood cells and culturing the cells (pg. 1945-1946)(limitations of Claim 2). After treatment the cells were subjected to in situ assays including the NT and TdT assay. For the NT assay, the cells were suspended with nick translation buffer, dATp, dGtp and dCTP and biotin-16-dUTP (pg. 1946, col. 1), the incubated with fluoresceinated avidin (limitations of Claim 8 and 9). For the TdT assay, fixed cells were suspended in a solution containing biotin-16-dUTP and dATP, dGTP and dCTP, this incubated with fluorescented avidin (limitations of Claims 8 and 9). Gorczyca teaches that the advantages of TdT or NT assays include the direct labeling of 3'-OH termini of the DNA breaks (pg. 1950, col. 2)(Limitation of Claim 6). Further, image analysis or flow cytometry was performed to detect fluorescence emissions from each cell and the data was stored and analyzed (pg. 1946, col. 1)(limitations of Claim 10).

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cherry in view of Marcon to include the labeling of the chromosomal fragments with biotin-16-dUTP and exposing to fluoresceinated avidin as taught by Gorczyca. The ordinary artisan would be motivated to have performed the method of Cherry in view of Marcon and labeled the fragments with biotin and fluoresceinated in order to allow rapid detection with flow cytometry and amenable to automation as taught by Gorczyca.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 1-17 are indefinite over the recitation "within the cell's nuclei" because it is unclear whether the chromosome fragments are analyzed within the cell nuclei or whether the chromosome fragments to be analyzed were previously found in the cell nuclei.

Conclusion

9. No claims allowable over the art.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
November 30, 2000

Lisa B Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600